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ORIGINAL ARTICLE

Effects of Inhaled Corticosteroids on Bone in Asthma Patients

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ABSTRACT

Background: Although inhaled corticosteroids are taken into the bloodstream, it is unclear how much damage they do to bones. The issue is crucial because 3% of people consistently use inhaled corticosteroids and could be doing for several decades.

Method: In 195 adults (118 women) with asthmatic, aged 25 to 45, we examined the dose-response relationship between total inhaled corticosteroid dosage and bone mineralization concentration at the lumbar region and proximal femur. Participants had received only a little amount of systemic steroids and had routinely used an inhaled corticosteroid for a minimum of six months. Multiple regression analysis was employed to evaluate the total dosage of inhaled corticosteroid's impact on the density of bones from surveys, computerized general practitioners' data, and printed and handwritten general medical documents.

Results: Treatment with inhaled corticosteroids lasted an average of 6 years (0–23), with a baseline total dose of 875 mg (87–4370). Both before and after adjusting for the influences of aging and gender, the results showed a negative correlation between the total dose of inhaled corticosteroid and skeletal mineral density at the lumbar region (L2-L4), femoral neck, and trochanter. An increase in inhaled corticosteroid dosage by twofold was linked to a 0•17 SD (95% CI 0•03-0•27) reduction in lumbar spine concentration of bone minerals... The femoral neck and trochanter all showed identical declines. The relationships remained strong after controlling for possible influencing variables such as regular exercise and previous use of oral, intranasal, cutaneous, and injectable corticosteroids.

Conclusion: This investigation shows a link between the overall average dosage of inhaled corticosteroids and decreased bone mineralization concentration in asthmatic sufferers.

Keywords: Corticosteroids, fracture, bone mineralization, inhaled, dosage, asthma, lumbar region, femur

INTRODUCTION

Asthma can be effectively treated with inhaled steroids, which are frequently needed for long-term management. In the U.S., 1 in 3 patients with asthma routinely inhales corticosteroids, with a quarter receiving 850 mg or more daily prescriptions. A corticosteroid can be administered through inhaling to the lungs with far fewer side consequences than by oral delivery. However, the administration of inhalation corticosteroids has been linked to bruises, cataracts, myopia, and to a more variable degree, absorption into the systemic bloodstream from the digestive tract than from the pulmonary [1]. It is unclear if and to which extent they affect skeletal in a medically significant way. Given the widespread usage of inhaled corticosteroids and the prevalence of fragility fractures, even a slight increase in the overall probability of osteoporosis might have significant effects on general healthcare.

Adolescent research looking at the relationship between inhaled corticosteroid usage and skeletal mineral content has shown mixed findings[2,3]. Most investigations were limited, the length of the medication was brief, and the majority were complicated by the individuals' prior usage of systemic corticosteroids. Consequently, using a significantly larger population of patients who had not previously used oral corticosteroids, we evaluated the assumption that there was a relationship between total combined inhaled corticosteroid usage and bone content at the lumbar region. We furthermore sought to determine the relationship after accounting for prospective confusing variables. To minimize confounding caused by menopausal and aging, we limited our investigation to individuals between the ages of 25 and 45.

METHODOLOGY

Subjects were selected from 49 general clinics in Pakistan that had computerized patient files and medicines going back at minimum 6 months. If their primary care records were accessible for data gathering, individuals were chosen from our registry of contributors for the asthma study. Individuals who met the admission requirements were found in the general practitioners' computerized records, and all patients were subjected to an assessment of their documented health records.

Participants were considered for the trial if they had previously been prescribed an inhaled corticosteroid continuously for a minimum of the previous six months, had a diagnosis of asthma, and were aged between the ages of 25 and 45. Individuals were disqualified if they'd previously used greater than two doses of oral corticosteroids, over two doses of injectable steroids, well over more than ten nasal corticosteroid inhalers, or even more than ten regimens of skin corticosteroids combined. Additionally, individuals were disqualified if they suffered from a disease and had either taken drugs that were thought to impair bone mineralization (other than having oral birth control pills).

Within such a 6-week timeframe, individuals visited the doctor's office twice. They filled out a survey and conducted pulmonary function testing by spirometry, and bronchodilator reversibility checks at the initial screening. The greatest value obtained from 3 consecutive measures taken with a dry-bellows spirometer while the subject was sitting was the forced expiration flow in 1 second (FEV1). The survey inquired about any ongoing medication use as well as any prior use of furosemide, estrogenic activity (particularly contraceptive pills), mineral supplements, vitamin D, fluoridated, and anabolic drugs as well as cortisone (breathed, oral, intravenous, intranasal, and topical). Ethnicity background, profession, date of asthma diagnosis, hospitalizations for asthma, the record of tobacco, additional present, and historical medical issues, prior fracturing, family background of hip fracture, and consumption of drink, tea, caffeine, and dairy items were all questioned. Females were questioned regarding their menstruation pattern, the number of babies, and hysterectomy. Regular exercise even during the participant's primary profession was assessed on a range of one to five for sitting, standing, moving around, and lifting weights. A revised form of the survey, which inquires about the regularity and length of frequent sports participation engaged during the previous year, was used to produce a fitness rating.

We considered the 3 inhaled corticosteroids (beclometasone, dipropionate, budesonide, and fluticasone propionate) to just be equally potent and did not bother to account for variations in composition, inhalers, or spacer gadgets since there is even now disagreement regarding the comparative systemic impacts of these medications. A research assistant who was not informed of the bone density characteristics calculated the daily average dosage and length of administration of each kind of steroid inhaler from the survey and verified it using the paper documents. Inhaled corticosteroid maximum dosage was given as mg (the product of an average daily dose of 365 duration yearly). Oral and injectable steroid prior use has been represented as sessions, nasal steroid prior use as canisters, and cutaneous steroid prior use as the quantity prescribed. The purpose of the next appointment was always to evaluate the patient's height, body weight, and lumbar vertebrae and femur neck bone mass

densities. By using double energy X-ray absorptiometry (DEXA), the bone density (g/cm3) at the left femur and A-P spinal (L2-L4) was calculated. Regular calibrating assessments were made, and they stayed constant all through the research. The individual was lying supine while the lateral spinal morphometry (T4-L4) was assessed [4,5]

By using multiple linear regression, we calculated the impact of the total dosage of inhaled corticosteroid on skeletal mineralization density inside the lumbar region (L2-L4) and proximate femur (SPSS version 25). For presumptive confounders of age and gender as well as total inhaled corticosteroid dosage, a basic design was constructed. For the relationship among total inhaled steroid dosage and bone density of minerals at L2-L4, we examined linear, log streamlined, reciprocity, and category modeling using modified r2 and the probability test, accordingly.

In some univariate analyses, we evaluated the impact of confounding variables on skeletal mineral density at L2-L4. The basic analysis was then fitted with each of the bone-mineral density-related factors (p<0•1) to ascertain their impact on the relationship between the total inhaled corticosteroid administration and skeletal mineral density. The aggregate dosage of inhaled corticosteroid, age, and gender then were included one at a time in the finished model as a multiplicative interacting effect. Ultimately, a completely modified model encompassing all factors connected to either continuous dosage of inhaled corticosteroid or bone-mineral density in univariate analysis was built. Following confirming that the bone-mineral density standard for the female in our study was consistent with an age-matched female, the shift in bone-mineral density was represented in g/cm2 and SD (no data accessible for males).

RESULTS

We looked at 195 participants (118 women, 77 men), 175 of whom were drawn from primary care and 21 through our registry of volunteers. Their average FEV1 was 92% expected, and their average lifespan was 31 (Table 1).

Table 1: Characteristics of patients

Characteristic	Total (n=195)	Male (n=77)	Female (n=118)
Demographic			
Age	31(28-35)	32(27-35)	35(28-34)
Height	167(160-173)	162(158-166)	177(170-180)
Weight	68(60-82)	63(55-70)	80(71-90)
Body mass index	23(22-26)	23(22-26)	25(23-27)
Status of smoking	29(15%)	18(16%)	9(12%)
Spirometry	92(14%)	95(15%)	88(15%)
Mean bone mineral density			
Lumbar	1.20(0.13)	1.22(0.13)	1.20(0.17)
Femur	1.04(0.13)	1.04(0.12)	1.06(0.14)
Trochanter	0.86(0.13)	0.84(0.12)	0.92(0.13)

The median total dosage of an inhaled corticosteroid is approximately 875 mg during 6 years of therapy (interquartile range: 0•6-23) (range 87–4370). Beclometasone dipropionate, budesonide, and fluticasone propionate were consumed by 156 (81%), 26 (13%), and 11 (5%), correspondingly, of the individuals at the moment of enrollment. The majority of individuals (150 [77%]) were already using metered-dose inhalers, while 21 (10%) were utilizing spacers. [6] (22%), 61 (31%), and 88 (44%) of the participants had previously completed one or more regimens of oral corticosteroids. In addition, 132 (67%) had used cutaneous corticosteroids, 88 (44%) had used intranasal corticosteroids, and 23 (11%) had used parenteral corticosteroids just once or twice. However, 111 (82%) of the former category had only ever obtained five doses or less.

Table 1 displays the average (SD) bone-mineral concentrations at the 4 locations. In the univariate analyses, the total estrogen dosage, total calcium consumption, body mass index, don't ever smoke, standing, walking, and carrying at the job were all linked to bone mineral density (table 2).

Table 2: Effect of a potential factor on bone mineral concentration at L2-L4 (univariate)

Characteristic	Regression coefficient	P
Demographic		
Age	0.15	0.03
Height	0.001	0.25
Weight	0.003	0.01
Sex	0.31	0.13
Body mass index	0.008	0.001
Status of smoking	0.040	0.04
Spirometry		
FEV1	0.000	0.56
Asthma admission (never vs ever)	0.027	0.36
Asthma duration	0.006	0.34
Physical activity		
Exercise rating	0.006	0.33
Stand	0.0023	0.061
Walk	0.022	0.097
Lift	0.002	0.027

Either prior or after adjusting for age and gender, there existed a negative linear relationship between both the logarithm of the total dosage of inhaled corticosteroid and the bone densities at the lumbar region, femur neck and trochanter. A twofold of the overall dosage of inhaled corticosteroid was linked to a 0•022 g/cm3 (95% CI 0•005-0•042) or 0•17 SD (0•03-0•27) reduction in bone mineral densities in the lumbar region, and consequences of comparable size were observed on the other 3 locations (table 3). This became our chosen final model because the relationship between the total dose of inhaled corticosteroid and bone mineral concentration remained unchanged after adjusting for the possible factors. The sexual connection did not significantly affect the impact of the dose levels of inhaled corticosteroids. The amount of the inhaled corticosteroid impact is likely, if something, to be bigger at all locations in the multivariable logistic model (table 3).

Table 3: Effect of the twofold total dosage of inhaled corticosteroids on lumbar and femur bone mineral concentration.

Characteristic	Mean (95% CI)	P
Lumbar spine (L2-L4)		
Age and gender	-0.022	0.011
All other	-0.031	0.002
Femur		
Age and gender	-0.020	0.028
All other	-0.025	0.014
Trochanter		
Age and gender	-0.019	0.024
All other	-0.025	0.009

The consequence of the total time of inhaled corticosteroid usage on the bone concentration of minerals was pretty much similar to the effects of dose levels when simulated similarly. Well at 4 locations, decreases in the bone concentration of between 0•017 and 0•022 g/cm3 were linked to increasing the period of inhaled corticosteroid use. After adjusting for gender and age the average daily dosage of inhaled corticosteroids was still not linked to a decline in bone mineral concentration. Spinal column morphologies on any patient did not reveal any fractures.

DISCUSSION

This extensive cross-sectional study examined the relationship between asthmatic sufferers' usage of inhaled corticosteroids and their bone mineral content. The aggregate inhaled corticosteroid dosage and bone mineralization density at the proximate femur and lumbar spinal were inversely correlated, according to our findings.

Our research was deliberately intended to overcome some of the issues with earlier research. We increased the representative sample by enlisting individuals from the primary-care community, and we reduced the possibility of age and

menopausal interference by limiting the trial to individuals aged 25 to 45. Individuals who had previously used little to no oral, intranasal, cutaneous, or injectable corticosteroids varied in age from 0 to 23 years, with a baseline of six years. In addition to the survey, we also acquired thorough prescribing information from computerized records and case records to reduce the likelihood of misclassification of prior corticosteroid consumption. While using a separate researcher who was not informed of the bone-mineral density information, we also reduced the possibility of biases when evaluating exposures to corticosteroids.

The research gives more accurate estimations of the impact of inhaled corticosteroids than earlier planned or cross-sectional investigations due to the magnitude, prolonged course of therapy, and consideration of complicating variables.

Because reduced regular exercise and growth among kids due to asthmatic may lower bone mass, an increasing asthmatic intensity is a possible potential issue.

Although the sample size we researched [7-9] had mild breathing problems with an average FEV1 of 92% predetermined, the impact of inhaled corticosteroid usages on bone-mineral density was unaffected by adjusting for our proxy identifiers of disease severity. As just a result, asthma intensity is highly improbable to have a significant confounder throughout this study (ie, regular exercise, FEV1, and hospital stay). Although it is uncertain if inhaled corticosteroids affect pubescent growth and subsequently maximal bone mass [10-12], this process is unclear to account for our results given that only 8% of our individuals had been using an inhaled corticosteroid before their [13,14].

Whereas one study indicates that cortical bone may be damaged to the same level, oral corticosteroids had traditionally been assumed to primarily impact trabecular bone[15,16]. Because the drop in bone mineral density at the proximal femur (which is primarily cortical bone) was still only marginally lower than that observed at the lumbar vertebrae, our data imply an impact on cortical bone in addition to trabeculae (dominantly trabecular bone). Our discovery of a decline in bone mass at the lumbar region is in line with the results of our earlier pilot testing. [17-19]Only among women, according to three other research, which includes our own, but this conclusion might be due to the small sample size. [20] Males and females did not vary in how inhaled corticosteroids affected bone mineralization density, according to our research.

According to our research, using inhaled corticosteroids is linked to a loss of bone mineral density in the spinal and proximate femur. Just at the lumbar region, femoral neck, and trochanter, the mean reduction related to twofold dose levels of inhaled corticosteroid indicated 0•17 SD, 0•13 SD, 0•17 SD, and 0•12 SD, respectively. Because 80% of the participants in our study used beclometasone dipropionate as their inhaled corticosteroid of choice, and the outcomes were identical whenever these participants were the only ones included in the analysis, the outcomes will mostly represent the impacts of this medication. People receiving a distinct inhaled corticosteroid may experience an impact of various sizes.

As an illustration, the extent of the response implies that the skeletal mineralization density at the lumbar region of an individual who has received 2000 g of an inhaled corticosteroid daily for seven years (5111 mg) would be 1 SD less than those of a person who has received 200 g daily for one year. Over a short period, such variations in bone density are unlikely to be significant, but long-term exposure to large dosages may have medically profound impacts.

According to statistics on elderly females, for instance, a 1 SD decrease in the density of bone minerals has been linked to a twofold chance of a fracture. [21] Participants in our research who have received large dosages of inhaled corticosteroids might have reduced bone mineral concentrations as they entered their 4th and 5th decades and are probably to need to keep taking inhaled corticosteroids. A minor increment in the incidence of fragility fractures might have a significant public-health consequence because more than half a million Pakistanis presently take 850 g upwards of an inhaled corticosteroid daily [19].

The dangers and advantages of any medication must be considered, and it is obvious that inhaled corticosteroids are very successful at controlling asthmatic and lowering the requirement for ingesting corticosteroids.

CONCLUSION

The research indicates that prolonged use of larger doses may increase the risk of osteoporosis, thus patients ought to take the minimum effective dose that still effectively manages their asthmatic. Individuals who must long-term use high dosages of an inhaled corticosteroid might need to think about preventive fracture prevention methods.

REFERENCES

1. Walsh LJ, Wong CA, Cooper S, Guhan AR, Pringle M, Tattersfield AE. Morbidity from asthma in relation to regular treatment: a community based study. Thorax. 1999 Apr 1;54(4):296-300.
2. Tattersfield AE, Harrison TW, Hubbard RB, Mortimer K. Safety of inhaled corticosteroids. Proceedings of the American Thoracic Society. 2004 Nov;1(3):171-5.
3. Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. European Respiratory Journal. 2009 Jul 1;34(1):13-6.
4. Pauwels RA, Löfdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. New England Journal of Medicine. 1999 Jun 24;340(25):1948-53.
5. Marcus MW, Müskens RP, Ramdas WD, Wolfs RC, De Jong PT, Vingerling JR, Hofman A, Stricker BH, Jansonius NM. Corticosteroids and Open-Angle Glaucoma in the Elderly. Drugs & aging. 2012 Dec;29(12):963-70.
6. Acar M, Gedizlioglu M, Koskderelioglu A, Ozturk F, Kilinc S, Talay N. Effect of high-dose intravenous methyl-prednisolone treatment on intraocular pressure in multiple sclerosis patients with relapse. European Neurology. 2012;68(1):20-2.
7. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. Current opinion in ophthalmology. 2000 Dec 1;11(6):478-83.
8. Skoner DP. Inhaled corticosteroids: Effects on growth and bone health. Annals of Allergy, Asthma & Immunology. 2016 Dec 1;117(6):595-600.
9. Mori H, Tanaka H, Ohno Y, Ito F, Funaguchi N, Endo J, La BL, Minatoguchi S. Effect of intermittent systemic corticosteroid on bone metabolism in bronchial asthma patients. Journal of Asthma. 2009 Jan 1;46(2):142-6.
10. Kumarathas I, Harsløf T, Andersen CU, Langdahl B, Hilberg O, Bjermer L, Løkke A. The risk of osteoporosis in patients with asthma. European clinical respiratory journal. 2020 Jan 1;7(1):1763612.
11. Fuhlbrigge AL, Kelly HW. Inhaled corticosteroids in children: effects on bone mineral density and growth. The Lancet Respiratory Medicine. 2014 Jun 1;2(6):487-96.
12. Aljubran SA, Whelan GJ, Glaum MC, Lockey RF. Osteoporosis in the at-risk asthmatic. Allergy. 2014 Nov;69(11):1429-39.
13. Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: room for improvement. Pulmonary pharmacology & therapeutics. 2007 Feb 1;20(1):23-35.
14. Anderson WJ, McFarlane LC, Lipworth BJ. Prospective follow-up of novel markers of bone turnover in persistent asthmatics exposed to low and high doses of inhaled ciclesonide over 12 months. The Journal of Clinical Endocrinology & Metabolism. 2012 Jun 1;97(6):1929-36.
15. Maspero J, Backer V, Yao R, Staudinger H, Teper A. Effects of mometasone, fluticasone, and montelukast on bone mineral density in adults with asthma. The Journal of Allergy and Clinical Immunology: In Practice. 2013 Nov 1;1(6):649-55.
16. Heffler E, Madeira LN, Ferrando M, Puggioni F, Racca F, Malvezzi L, Passalacqua G, Canonica GW. Inhaled corticosteroids safety and adverse effects in patients with asthma. The Journal of Allergy and Clinical Immunology: In Practice. 2018 May 1;6(3):776-81.
17. Watanabe H, Sugiyama K, Otsuji N, Nakano K, Arifuku H, Wakayama T, Tokita S, Koyama K, Hirata H, Arima M, Kurasawa K. Effect of inhaled corticosteroids on bone mineral density in patients with asthma. Asian Pacific Journal of Allergy and Immunology. 2020 May 17.
18. Yanik B, Ayrim A, Ozol D, Koktener A, Gokmen D. Influence of obesity on bone mineral density in postmenopausal asthma patients undergoing treatment with inhaled corticosteroids. Clinics. 2009;64:313-8.
19. Gatti D, Senna G, Viapiana O, Rossini M, Passalacqua G, Adami S. Allergy and the bone: unexpected relationships. Annals of Allergy, Asthma & Immunology. 2011 Sep 1;107(3):202-6.
20. Frampton GK, Shepherd J. Patient-reported outcomes in clinical trials of inhaled asthma medications: systematic review and research needs. Quality of Life Research. 2011 Apr;20(3):343-57.
21. Mainz JG, Sauner D, Malich A, John S, Beyermann H, Mentzel HJ, Kaiser WA, Zintl F. Cross-sectional study on bone density-related sonographic parameters in children with asthma: correlation to therapy with inhaled corticosteroids and disease severity. Journal of bone and mineral metabolism. 2008 Sep;26(5):485-92.